```
=> s nitric(3a)oxide(p)(donor# or agonist#) and insulin(p)(sensitiv? or resistan?)
        116377 NITRIC
       1241324 OXIDE
        152194 DONOR#
        108444 AGONIST#
          5875 NITRIC(3A)OXIDE(P)(DONOR# OR AGONIST#)
        138450 INSULIN
        773916 SENSITIV?
       1091033 RESISTAN?
         22051 INSULIN(P)(SENSITIV? OR RESISTAN?)
L1          36 NITRIC(3A)OXIDE(P)(DONOR# OR AGONIST#) AND INSULIN(P)(SENSITIV?
               OR RESISTAN?)

=> s l1 and py <=1998
      18913807 PY <=1998
L2          19 L1 AND PY <=1998

=> d l2 abs ibib kwic 1-19

L2   ANSWER 1 OF 19  CAPLUS  COPYRIGHT 2002 ACS
AB   A review with 40 refs., focusing on the actions of NO in skeletal muscle
     metab.  NO is a vasoactive substance, which was 1st described as
     endothelium-derived relaxing factor (EDRF).  Subsequently, NO has been
     found to be a messenger mol. abundantly present in the nervous system.
     Functioning as a neurotransmitter in the peripheral nervous system, NO
     mediates an array of physiol. functions such as gastrointestinal motility,
     regional blood flow, smooth muscle contraction, neuroendocrine activity,
     and immune function.  Recently, NO biosynthesis has been found in skeletal
     muscle, where NO exerts an effect on both the metabolic and contractile
     processes.  NO donors have been shown to increase glucose
     transport in skeletal muscle.  Inhibition of nitric
     oxide synthase activity blunts contraction-stimulated glucose
     transport but has no effect on insulin-stimulated glucose
     transport.  NOS protein expression is enhanced by chronic exercise
     suggesting that NO may play a role in the improved glucose tolerance and
     increased insulin sensitivity characteristic of the
     trained state.
ACCESSION NUMBER:         1998:696549  CAPLUS
DOCUMENT NUMBER:          130:79017
TITLE:                    Role of nitric oxide in contraction induced glucose
                          transport
AUTHOR(S):                Balon, Thomas W.
CORPORATE SOURCE:         Department of Diabetes, Endocrinology, and Metabolism,
                          City of Hope National Medical Center, Duarte, CA,
                          91010, USA
SOURCE:                   Adv. Exp. Med. Biol. (1998), 441(Drugs of
                          Abuse, Immunomodulation, and AIDS), 87-95
                          CODEN: AEMBAP; ISSN: 0065-2598
PUBLISHER:                Plenum Publishing Corp.
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
REFERENCE COUNT:          40    THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
SO   Adv. Exp. Med. Biol. (1998), 441(Drugs of Abuse,
     Immunomodulation, and AIDS), 87-95
     CODEN: AEMBAP; ISSN: 0065-2598
AB   A review with 40 refs., focusing on the actions of NO in skeletal muscle
```

metab. NO is a vasoactive substance, which was 1st described as endothelium-derived relaxing factor (EDRF). Subsequently, NO has been found to be a messenger mol. abundantly present in the nervous system. Functioning as a neurotransmitter in the peripheral nervous system, NO mediates an array of physiol. functions such as gastrointestinal motility, regional blood flow, smooth muscle contraction, neuroendocrine activity, and immune function. Recently, NO biosynthesis has been found in skeletal muscle, where NO exerts an effect on both the metabolic and contractile processes. NO **donors** have been shown to increase glucose transport in skeletal muscle. Inhibition of **nitric oxide** synthase activity blunts contraction-stimulated glucose transport but has no effect on **insulin**-stimulated glucose transport. NOS protein expression is enhanced by chronic exercise suggesting that NO may play a role in the improved glucose tolerance and increased **insulin sensitivity** characteristic of the trained state.

L2 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB The effects of **nitric oxide** (NO) on vascular reactivity and platelet function in the obese (cp/cp) and lean (+/) JCR:LA-cp rats were investigated. Phenylephrine (PE; 0.1 nM - 10 .mu.M) induced contraction of isolated aortic rings in both genotypes (cp/cp and +/) of JCR:LA-cp rats. The **sensitivity** to contraction with PE was enhanced in cp/cp compared with +/ rings. Rings from both genotypes showed an increased contraction upon removal of the endothelium. Acetylcholine (ACh; 0.1 nM - 10 .mu.M)-induced endothelium-dependent relaxation of rings was not significantly different in the two genotypes. Both were inhibited to a similar extent by NG-nitro-L-arginine Me ester (L-NAME; 0.01-1 mM) when administered in vitro. The **nitric oxide** synthase (NOS) inhibitor (L-NAME; 0.3, 1 or 3 mg ml-1, p.o.) when administered in vivo increased blood pressure in cp/cp rats but not in +/ rats. L-NAME resulted in greater inhibition of ACh-induced relaxation in cp/cp rings compared with +/ rings. L-NAME treatment in vivo caused a decrease in cGMP and NOS activity in rings from cp/cp but not +/ rats. The NO **donor**, S-nitroso-N-acetyl-DL-penicillamine (SNAP; 0.1 nM - 10 .mu.M)-induced relaxation of rings from +/ rats, an effect enhanced by the treatment with L-NAME in vivo. Oral administration of L-NAME did not enhance the vasorelaxant effect of SNAP on rings of aorta from cp/cp animals. Platelet aggregation and NOS activity were similar in both genotypes and were not modified by oral administration of L-NAME. These results show that unimpaired generation of NO is crucial for maintenance of vascular tone particularly under conditions of vascular insult exemplified by **insulin resistance**, obesity and dyslipidemia detected in cp/cp rats.

ACCESSION NUMBER: 1998:367381 CAPLUS
DOCUMENT NUMBER: 129:107569
TITLE: Inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, obese JCR:LA-cp rats
AUTHOR(S): Mckendrick, Joyce D.; Salas, Eduardo; Dube, Gregory P.; Murat, Jesus; Russell, James C.; Radomski, Marek W.
CORPORATE SOURCE: Department of Surgery, University of Alberta, Edmonton, T6G 2H7, Can.
SOURCE: British Journal of Pharmacology (**1998**), 124(2), 361-369
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press

09/806,989

DOCUMENT TYPE: Journal
LANGUAGE: English

TI Inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, obese JCR:LA-cp rats

SO British Journal of Pharmacology (**1998**), 124(2), 361-369
CODEN: BJPCBM; ISSN: 0007-1188

AB The effects of **nitric oxide** (NO) on vascular reactivity and platelet function in the obese (cp/cp) and lean (+/) JCR:LA-cp rats were investigated. Phenylephrine (PE; 0.1 nM - 10 .mu.M) induced contraction of isolated aortic rings in both genotypes (cp/cp and +/) of JCR:LA-cp rats. The **sensitivity** to contraction with PE was enhanced in cp/cp compared with +/ rings. Rings from both genotypes showed an increased contraction upon removal of the endothelium. Acetylcholine (ACh; 0.1 nM - 10 .mu.M)-induced endothelium-dependent relaxation of rings was not significantly different in the two genotypes. Both were inhibited to a similar extent by NG-nitro-L-arginine Me ester (L-NAME; 0.01-1 mM) when administered in vitro. The **nitric oxide** synthase (NOS) inhibitor (L-NAME; 0.3, 1 or 3 mg ml-1, p.o.) when administered in vivo increased blood pressure in cp/cp rats but not in +/ rats. L-NAME resulted in greater inhibition of ACh-induced relaxation in cp/cp rings compared with +/ rings. L-NAME treatment in vivo caused a decrease in cGMP and NOS activity in rings from cp/cp but not +/ rats. The NO **donor**, S-nitroso-N-acetyl-DL-penicillamine (SNAP; 0.1 nM - 10 .mu.M)-induced relaxation of rings from +/ rats, an effect enhanced by the treatment with L-NAME in vivo. Oral administration of L-NAME did not enhance the vasorelaxant effect of SNAP on rings of aorta from cp/cp animals. Platelet aggregation and NOS activity were similar in both genotypes and were not modified by oral administration of L-NAME. These results show that unimpaired generation of NO is crucial for maintenance of vascular tone particularly under conditions of vascular insult exemplified by **insulin resistance**, obesity and dyslipidemia detected in cp/cp rats.

ST nitric oxide vasculodysfunction **insulin resistance** obesity; vascular dysfunction **insulin resistance** nitric oxide

IT Platelet (blood)
(aggregation; inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, obese JCR:LA-cp rats)

IT Artery
(aorta; inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, obese JCR:LA-cp rats)

IT Platelet (blood)
(cGMP; inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, obese JCR:LA-cp rats)

IT Blood vessel, disease
(dysfunction; inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, obese JCR:LA-cp rats)

IT Lipids, biological studies
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(dyslipidemia; inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, obese JCR:LA-cp rats)

IT Blood vessel

(endothelium; inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, obese JCR:LA-cp rats)

IT Obesity
(genetic; inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, obese JCR:LA-cp rats)

IT Blood pressure
Genotypes
Vasoconstriction
Vasodilation
(inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, obese JCR:LA-cp rats)

IT Cell aggregation
(platelet; inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, obese JCR:LA-cp rats)

IT 59-42-7, Phenylephrine
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(-induced contraction; inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, obese JCR:LA-cp rats)

IT 51-84-3, Acetylcholine, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(-induced relaxation; inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, obese JCR:LA-cp rats)

IT 10102-43-9, Nitric oxide, biological studies
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, obese JCR:LA-cp rats)

IT 125978-95-2, Nitric oxide synthetase
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, obese JCR:LA-cp rats)

IT 7665-99-8, CGMP
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(platelet; inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, obese JCR:LA-cp rats)

IT 9004-10-8
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**resistance**; inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, obese JCR:LA-cp rats)

IT 9004-10-8, **Insulin**, biological studies
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**resistance**; inhibition of nitric oxide generation unmasks vascular dysfunction in **insulin-resistant**, obese JCR:LA-cp rats)

L2 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB Aortic rings from the title rat were more sensitive to the contractile action of phenylephrine, a selective .alpha.1-adrenergic receptor **agonist**, than control rats. Acetylcholine-induced relaxation of phenylephrine-contracted aortic rings was similar in the title and control rats. However, its inhibition by L-NAME, a **nitric oxide** synthase (NOS) inhibitor, and L-NAME-induced increase in blood pressure were significantly greater in the title rats than in controls. The activity of NOS and bioactivity of NO as assessed by citrulline assay and cGMP content, resp., decreased only in the title rats.

ACCESSION NUMBER: 1998:367124 CAPLUS
DOCUMENT NUMBER: 129:134515
TITLE: Vascular wall function in the **insulin resistant** and atherosclerosis-prone JCR:LA-cp rat
AUTHOR(S): Russell, James C.; Mckendrick, Joyce D.; Radomski, Marek W.
CORPORATE SOURCE: Department of Surgery, University of Alberta, Edmonton, AB, T6G 2S2, Can.
SOURCE: Portland Press Proc. (**1998**), 15(Biology of Nitric Oxide, Part 6), 145
CODEN: POPPEF; ISSN: 0966-4068
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
TI Vascular wall function in the **insulin resistant** and atherosclerosis-prone JCR:LA-cp rat
SO Portland Press Proc. (**1998**), 15(Biology of Nitric Oxide, Part 6), 145
CODEN: POPPEF; ISSN: 0966-4068
AB Aortic rings from the title rat were more sensitive to the contractile action of phenylephrine, a selective .alpha.1-adrenergic receptor **agonist**, than control rats. Acetylcholine-induced relaxation of phenylephrine-contracted aortic rings was similar in the title and control rats. However, its inhibition by L-NAME, a **nitric oxide** synthase (NOS) inhibitor, and L-NAME-induced increase in blood pressure were significantly greater in the title rats than in controls. The activity of NOS and bioactivity of NO as assessed by citrulline assay and cGMP content, resp., decreased only in the title rats.
ST vascular wall function **insulin resistance** atherosclerosis
IT Aorta
Atherosclerosis
Insulin resistance
Vasoconstriction
Vasodilation
(vascular wall function in **insulin-resistant** and atherosclerosis-prone JCR:LA-cp rat)
IT Blood pressure
(vascular wall function in **insulin-resistant** and atherosclerosis-prone JCR:LA-cp rat in relation to)
IT .alpha.1-Adrenoceptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(vasoconstriction induced via; vascular wall function in **insulin-resistant** and atherosclerosis-prone JCR:LA-cp rat)
IT 9004-10-8, **Insulin**, biological studies
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or

effector, except adverse); BIOL (Biological study)
(**resistance**; vascular wall function in **insulin-resistant** and atherosclerosis-prone JCR:LA-cp rat)

IT 10102-43-9, Nitric oxide, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(vascular wall function in **insulin-resistant** and atherosclerosis-prone JCR:LA-cp rat in relation to)

IT 125978-95-2, Nitric oxide synthetase
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(vascular wall function in **insulin-resistant** and atherosclerosis-prone JCR:LA-cp rat in relation to)

IT 7665-99-8, CGMP
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(vascular wall function in **insulin-resistant** and atherosclerosis-prone JCR:LA-cp rat in relation to)

IT 59-42-7, Phenylephrine
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(vasoconstriction induced by; vascular wall function in **insulin-resistant** and atherosclerosis-prone JCR:LA-cp rat)

IT 51-84-3, Acetylcholine, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(vasodilation induced by; vascular wall function in **insulin-resistant** and atherosclerosis-prone JCR:LA-cp rat)

L2 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB Several hypertensive states are assocd. with **resistance** to **insulin**-induced glucose disposal and **insulin**-induced vasodilation. **Insulin** can inhibit vascular smooth muscle (VSM) contraction at the level of the VSM cell, and **resistance** to **insulin**'s inhibition of VSM cell contraction may be of pathophysiol. importance. To understand the VSM cellular mechanisms by which **insulin resistance** leads to increased VSM contraction, the authors sought to det. how **insulin** inhibits contraction of normal VSM. It has been shown that **insulin** lowers the contractile **agonist**-stimulated intracellular Ca2+ (Cai2+) transient in VSM cells. In this study, the authors' goal was to see whether **insulin** inhibits VSM cell contraction at steps distal to Cai2+ and, if so, to det. whether the mechanism is dependent on **nitric oxide** synthase (NOS) and cGMP. Primary cultured VSM cells from canine femoral artery were bathed in a physiol. concn. of extracellular Ca2+ and permeabilized to Ca2+ with a Ca2+ ionophore, either ionomycin or A-23187. The resultant increase in Cai2+ contracted individual cells, as measured by photomicroscopy. Preincubating cells with 1 nM **insulin** for 30 min did not affect basal Cai2+ or the ionomycin-induced increase in Cai2+, as detd. by fura 2 fluorescence measurements, but it did inhibit ionomycin- and A-23187-induced contractions by 47 and 51%, resp. (both). In the presence of 1.0 .mu.M ionized Ca2+, ionomycin-induced contractions were inhibited by **insulin** in a dose-dependent manner. In the presence of ionomycin, **insulin** increased cGMP prodn. by 43%. 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (10 .mu.M), a selective inhibitor of guanylate cyclase that blocked cGMP prodn. in these cells, completely blocked the inhibition by **insulin** of ionomycin-induced contraction. The cells

expressed the inducible isoform of NOS. NG-monomethyl-L-arginine or NG-nitro-L-arginine Me ester (0.1 mM), inhibitors of NOS, did not affect ionomycin-induced contraction but prevented **insulin** from inhibiting contraction. The authors conclude that **insulin** stimulates cGMP prodn. and inhibits VSM contraction in the presence of elevated Cai2+. This inhibition by **insulin** of VSM contraction at sites where Cai2+ could not be rate limiting is dependent on NOS and cGMP.

ACCESSION NUMBER: 1998:350140 CAPLUS
DOCUMENT NUMBER: 129:76805
TITLE: Insulin inhibits vascular smooth muscle contraction at a site distal to intracellular Ca2+ concentration
AUTHOR(S): Kahn, Andrew M.; Husid, Annat; Odebunmi, Timothy; Allen, Julius C.; Seidel, Charles L.; Song, Tom
CORPORATE SOURCE: Department of Medicine, The University of Texas Health Science Center, Houston, TX, 77030, USA
SOURCE: Am. J. Physiol. (**1998**), 274(5, Pt. 1), E885-E892
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Am. J. Physiol. (**1998**), 274(5, Pt. 1), E885-E892
CODEN: AJPHAP; ISSN: 0002-9513
AB Several hypertensive states are assocd. with **resistance** to **insulin**-induced glucose disposal and **insulin**-induced vasodilation. **Insulin** can inhibit vascular smooth muscle (VSM) contraction at the level of the VSM cell, and **resistance** to **insulin**'s inhibition of VSM cell contraction may be of pathophysiol. importance. To understand the VSM cellular mechanisms by which **insulin resistance** leads to increased VSM contraction, the authors sought to det. how **insulin** inhibits contraction of normal VSM. It has been shown that **insulin** lowers the contractile **agonist**-stimulated intracellular Ca2+ (Cai2+) transient in VSM cells. In this study, the authors' goal was to see whether **insulin** inhibits VSM cell contraction at steps distal to Cai2+ and, if so, to det. whether the mechanism is dependent on **nitric oxide** synthase (NOS) and cGMP. Primary cultured VSM cells from canine femoral artery were bathed in a physiol. concn. of extracellular Ca2+ and permeabilized to Ca2+ with a Ca2+ ionophore, either ionomycin or A-23187. The resultant increase in Cai2+ contracted individual cells, as measured by photomicroscopy. Preincubating cells with 1 nM **insulin** for 30 min did not affect basal Cai2+ or the ionomycin-induced increase in Cai2+, as detd. by fura 2 fluorescence measurements, but it did inhibit ionomycin- and A-23187-induced contractions by 47 and 51%, resp. (both). In the presence of 1.0 .mu.M ionized Ca2+, ionomycin-induced contractions were inhibited by **insulin** in a dose-dependent manner. In the presence of ionomycin, **insulin** increased cGMP prodn. by 43%. 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (10 .mu.M), a selective inhibitor of guanylate cyclase that blocked cGMP prodn. in these cells, completely blocked the inhibition by **insulin** of ionomycin-induced contraction. The cells expressed the inducible isoform of NOS. NG-monomethyl-L-arginine or NG-nitro-L-arginine Me ester (0.1 mM), inhibitors of NOS, did not affect ionomycin-induced contraction but prevented **insulin** from inhibiting contraction. The authors conclude that **insulin** stimulates cGMP prodn. and inhibits VSM contraction in the presence of elevated Cai2+. This inhibition by **insulin** of VSM contraction

at sites where Cai2+ could not be rate limiting is dependent on NOS and cGMP.

IT **Insulin resistance**
Signal transduction (biological)
Vascular smooth muscle
Vasoconstriction
(**insulin** inhibits canine vascular smooth muscle contraction at site distal to intracellular calcium concn. and is dependent on nitric oxide synthase and cGMP)

L2 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB **Nitric oxide** activates guanylate cyclase to form cGMP, comprising a signaling system that is believed to be a distinct mechanism for increasing glucose transport and metab. in skeletal muscle. The effects of a selective cGMP phosphodiesterase inhibitor, zaprinast, on basal glucose utilization was investigated in incubated rat soleus muscle prepns. isolated from both **insulin-sensitive** (lean Zucker; Fa/) and **insulin-resistant** (obese Zucker; fa/fa) rats. Zaprinast at 27 .mu.M significantly increased cGMP levels in incubated soleus muscle isolated from lean, but not obese, Zucker rats. Muscles were incubated with 14C-labeled glucose and various concns. of zaprinast (3, 27 and 243 .mu.M). Zaprinast (at 27 and 243 .mu.M) significantly increased rates of net and 14C-labeled lactate release and of glycogen synthesis in lean Zucker rat soleus muscle; glucose oxidn. was also increased by 27 .mu.M zaprinast. In addn., regardless of concn., the phosphodiesterase inhibitor failed to increase any aspect of 14C-labeled glucose utilization in soleus muscles isolated from obese Zucker rats. The maximal activity of **nitric oxide** synthase (NOS) was significantly decreased in **insulin-resistant** obese Zucker muscles. Thus the lack of effect of zaprinast in **insulin -resistant** skeletal muscle is consistent with decreased NOS activity. To test whether there is a defect in **insulin-resistant** skeletal muscle for endogenous activation of guanylate cyclase, soleus muscles were isolated from both **insulin-sensitive** and **insulin-resistant** Zucker rats and incubated with various concns. of the NO **donor** sodium nitroprusside (SNP; 0.1, 1, 5 and 15 mM). SNP significantly increased rates of net and 14C-labeled lactate release, as well as glucose oxidn. in muscles isolated from both **insulin-sensitive** and **insulin-resistant** rats. A decreased response to SNP was obsd. in the dose-dependent generation of cGMP within isolated soleus muscles from **insulin-resistant** rats. A possible link between impaired NO/cGMP signaling and abnormal glucose utilization by skeletal muscle is discussed.

ACCESSION NUMBER: 1998:51319 CAPLUS
DOCUMENT NUMBER: 128:152563
TITLE: Evidence for altered **sensitivity** of the nitric oxide/cGMP signaling cascade in **insulin -resistant** skeletal muscle
AUTHOR(S): Young, Martin E.; Leighton, Brendan
CORPORATE SOURCE: Department of Biochemistry, University of Oxford, Oxford, OX1 3QU, UK
SOURCE: Biochemical Journal (**1998**), 329(1), 73-79
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Evidence for altered **sensitivity** of the nitric oxide/cGMP

signaling cascade in **insulin-resistant** skeletal muscle

SO Biochemical Journal (**1998**), 329(1), 73-79
CODEN: BIJOAK; ISSN: 0264-6021

AB **Nitric oxide** activates guanylate cyclase to form cGMP, comprising a signaling system that is believed to be a distinct mechanism for increasing glucose transport and metab. in skeletal muscle. The effects of a selective cGMP phosphodiesterase inhibitor, zaprinast, on basal glucose utilization was investigated in incubated rat soleus muscle prepns. isolated from both **insulin-sensitive** (lean Zucker; Fa/) and **insulin-resistant** (obese Zucker; fa/fa) rats. Zaprinast at 27 .mu.M significantly increased cGMP levels in incubated soleus muscle isolated from lean, but not obese, Zucker rats. Muscles were incubated with 14C-labeled glucose and various concns. of zaprinast (3, 27 and 243 .mu.M). Zaprinast (at 27 and 243 .mu.M) significantly increased rates of net and 14C-labeled lactate release and of glycogen synthesis in lean Zucker rat soleus muscle; glucose oxidn. was also increased by 27 .mu.M zaprinast. In addn., regardless of concn., the phosphodiesterase inhibitor failed to increase any aspect of 14C-labeled glucose utilization in soleus muscles isolated from obese Zucker rats. The maximal activity of **nitric oxide** synthase (NOS) was significantly decreased in **insulin-resistant** obese Zucker muscles. Thus the lack of effect of zaprinast in **insulin-resistant** skeletal muscle is consistent with decreased NOS activity. To test whether there is a defect in **insulin-resistant** skeletal muscle for endogenous activation of guanylate cyclase, soleus muscles were isolated from both **insulin-sensitive** and **insulin-resistant** Zucker rats and incubated with various concns. of the NO **donor** sodium nitroprusside (SNP; 0.1, 1, 5 and 15 mM). SNP significantly increased rates of net and 14C-labeled lactate release, as well as glucose oxidn. in muscles isolated from both **insulin-sensitive** and **insulin-resistant** rats. A decreased response to SNP was obsd. in the dose-dependent generation of cGMP within isolated soleus muscles from **insulin-resistant** rats. A possible link between impaired NO/cGMP signaling and abnormal glucose utilization by skeletal muscle is discussed.

ST **insulin resistance** muscle nitric oxide cGMP; signaling nitric oxide muscle **insulin resistance**

IT Oxidation
(biol., glucose; evidence for altered **sensitivity** of nitric oxide/cGMP signaling cascade in **insulin-resistant** skeletal muscle)

IT Signal transduction, biological
(evidence for altered **sensitivity** of nitric oxide/cGMP signaling cascade in **insulin-resistant** skeletal muscle)

IT Obesity
(genetic; evidence for altered **sensitivity** of nitric oxide/cGMP signaling cascade in **insulin-resistant** skeletal muscle)

IT Secretion (process)
(lactate; evidence for altered **sensitivity** of nitric oxide/cGMP signaling cascade in **insulin-resistant** skeletal muscle)

IT Carbohydrates, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metab., glucose; evidence for altered **sensitivity** of nitric oxide/cGMP signaling cascade in **insulin-resistant**

skeletal muscle)
IT Muscle
(soleus; evidence for altered **sensitivity** of nitric oxide/cGMP signaling cascade in **insulin-resistant** skeletal muscle)
IT 10102-43-9, Nitric oxide, biological studies
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(evidence for altered **sensitivity** of nitric oxide/cGMP signaling cascade in **insulin-resistant** skeletal muscle)
IT 9054-75-5, Guanylate cyclase 9068-52-4, CGMP phosphodiesterase 125978-95-2, Nitric oxide synthetase
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(evidence for altered **sensitivity** of nitric oxide/cGMP signaling cascade in **insulin-resistant** skeletal muscle)
IT 7665-99-8, CGMP
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(evidence for altered **sensitivity** of nitric oxide/cGMP signaling cascade in **insulin-resistant** skeletal muscle)
IT 50-99-7, D-Glucose, biological studies
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BIOL (Biological study); PROC (Process)
(evidence for altered **sensitivity** of nitric oxide/cGMP signaling cascade in **insulin-resistant** skeletal muscle)
IT 50-21-5, Lactic acid, biological studies
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(evidence for altered **sensitivity** of nitric oxide/cGMP signaling cascade in **insulin-resistant** skeletal muscle)
IT 9005-79-2, Glycogen, biological studies
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(evidence for altered **sensitivity** of nitric oxide/cGMP signaling cascade in **insulin-resistant** skeletal muscle)
IT 9004-10-8
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**resistance**; evidence for altered **sensitivity** of nitric oxide/cGMP signaling cascade in **insulin-resistant** skeletal muscle)
IT 9004-10-8, **Insulin**, biological studies
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**resistance**; evidence for altered **sensitivity** of nitric oxide/cGMP signaling cascade in **insulin-resistant** skeletal muscle)

L2 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2002 ACS
AB We investigated whether endothelial function may be impaired in the Otsuka

Long-Evans Tokushima Fatty (OLETF) rat, a model of spontaneous NIDDM. The effect of exercise training and food restriction on endothelial function was also studied. OLETF rats were divided into three groups at age 16 wk: sedentary, exercise trained, and food restricted (70% of the food intake of sedentary rats). Otsuka Long-Evans Tokushima rats were used as the age-matched nondiabetic controls. Endothelium-dependent relaxation of the thoracic aorta induced by histamine was significantly attenuated in the sedentary or food-restricted rats, and exercise training improved endothelial function. Relaxation induced by sodium nitroprusside, a **donor** of **nitric oxide**, did not differ significantly among groups. Both exercise training and food restriction significantly suppressed plasma levels of glucose and **insulin** and serum levels of triacylglycerol and cholesterol and reduced the accumulation of abdominal fat. **Insulin sensitivity**, as measured by the hyperinsulinemic-euglycemic clamp technique, was significantly decreased in sedentary rats but was enhanced in exercise-trained and food-restricted rats. The urinary excretion of nitrite was significantly decreased in sedentary and food-restricted rats compared with nondiabetic rats and was significantly increased in exercise-trained rats. These results indicate that exercise training, but not food restriction, prevents endothelial dysfunction in NIDDM rats, presumably due to the exercise-induced increase in the prodn. of **nitric oxide**.

ACCESSION NUMBER: 1998:29215 CAPLUS
DOCUMENT NUMBER: 128:126599
TITLE: Effect of exercise training and food restriction on endothelium-dependent relaxation in the Qtsuka Long-Evans Tokushima fatty rat, a model of spontaneous NIDDM
AUTHOR(S): Sakamoto, Sadaichi; Minami, Kazushi; Niwa, Yasuharu; Ohnaka, Masaharu; Nakaya, Yutaka; Mizuno, Akira; Kuwajima, Masamichi; Shima, Kenji
CORPORATE SOURCE: Departments of Nutrition, University of Tokushima, Tokushima City, 770, Japan
SOURCE: Diabetes (**1998**), 47(1), 82-86
CODEN: DIAEAZ; ISSN: 0012-1797
PUBLISHER: American Diabetes Association
DOCUMENT TYPE: Journal
LANGUAGE: English

SO Diabetes (**1998**), 47(1), 82-86
CODEN: DIAEAZ; ISSN: 0012-1797

AB We investigated whether endothelial function may be impaired in the Otsuka Long-Evans Tokushima Fatty (OLETF) rat, a model of spontaneous NIDDM. The effect of exercise training and food restriction on endothelial function was also studied. OLETF rats were divided into three groups at age 16 wk: sedentary, exercise trained, and food restricted (70% of the food intake of sedentary rats). Otsuka Long-Evans Tokushima rats were used as the age-matched nondiabetic controls. Endothelium-dependent relaxation of the thoracic aorta induced by histamine was significantly attenuated in the sedentary or food-restricted rats, and exercise training improved endothelial function. Relaxation induced by sodium nitroprusside, a **donor** of **nitric oxide**, did not differ significantly among groups. Both exercise training and food restriction significantly suppressed plasma levels of glucose and **insulin** and serum levels of triacylglycerol and cholesterol and reduced the accumulation of abdominal fat. **Insulin sensitivity**, as measured by the hyperinsulinemic-euglycemic clamp technique, was significantly decreased in sedentary rats but was enhanced in

exercise-trained and food-restricted rats. The urinary excretion of nitrite was significantly decreased in sedentary and food-restricted rats compared with nondiabetic rats and was significantly increased in exercise-trained rats. These results indicate that exercise training, but not food restriction, prevents endothelial dysfunction in NIDDM rats, presumably due to the exercise-induced increase in the prodn. of **nitric oxide**.

L2 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB To investigate whether **insulin** effect on endothelium is related to a specific signal transduction pathway or reflects a more generalized action of the hormone, we studied in aortic rings of Wistar-Kyoto (WKY) rats the effects of the hormone on endothelium-dependent relaxations generated by acetylcholine, ADP, the selective .alpha.2-adrenergic **agonist** UK 14304, and the calcium ionophore ionomycin. The responses were evaluated both in control conditions and after 30 min of exposure to three different levels of **insulin** (30, 100, and 500 .mu.U/mL). **Insulin** failed to modify the phenylephrine aortic contractions and the relaxations induced by acetylcholine, ADP, and ionomycin. In contrast, both 100 and 500 .mu.U/mL **insulin** were able to potentiate the UK 14304-induced vasorelaxation (+96% and +91%, resp.). Pertussis toxin, which causes .alpha.2-adrenergic receptor Gi uncoupling, reduced the .alpha.2-adrenergic vasorelaxation and prevented the **insulin** potentiation of the response to UK 14304. Furthermore, in primary cultured aortic endothelial cells from WKY, we evaluated the conversion of [3H]arginine to [3H]citrulline in response to acetylcholine, ionomycin, and UK 14304, both in control conditions and during **insulin** exposure. Again, **insulin** did not affect basal citrulline prodn. or the increase induced by acetylcholine and ionomycin, whereas it potentiated the response to UK 14304. Finally, in aortic rings of spontaneously hypertensive rats, **insulin** treatment (100 and 500 .mu.U/mL) was unable to enhance the .alpha.2-adrenergic vasodilator response; in vascular endothelial cells from spontaneously hypertensive rats, **insulin** did not potentiate the increase in citrulline prodn. evoked by UK 14304. In conclusion, **insulin** selectively enhances .alpha.2-adrenergic endothelial vasorelaxation through a pertussis toxin-**sensitive** mechanism, by potentiating endothelial **nitric oxide** prodn. This vasorelaxant mechanism is altered in spontaneously hypertensive rats.

ACCESSION NUMBER: 1997:738242 CAPLUS
DOCUMENT NUMBER: 128:18893
TITLE: Insulin enhances endothelial .alpha.2-adrenergic vasorelaxation by a pertussis toxin mechanism
AUTHOR(S): Lembo, Giuseppe; Iaccarino, Guido; Vecchione, Carmine; Barbato, Emanuele; Morisco, Carmine; Monti, Francesco; Parrella, Lucia; Trimarco, Bruno
CORPORATE SOURCE: IRCCS "Neuromed," Pozzilli (IS), Italy
SOURCE: Hypertension (Dallas) (**1997**), 30(5), 1128-1134
CODEN: HPRTDN; ISSN: 0194-911X
PUBLISHER: American Heart Association
DOCUMENT TYPE: Journal
LANGUAGE: English

SO Hypertension (Dallas) (**1997**), 30(5), 1128-1134
CODEN: HPRTDN; ISSN: 0194-911X

AB To investigate whether **insulin** effect on endothelium is related to a specific signal transduction pathway or reflects a more generalized action of the hormone, we studied in aortic rings of Wistar-Kyoto (WKY)

rats the effects of the hormone on endothelium-dependent relaxations generated by acetylcholine, ADP, the selective .alpha.2-adrenergic **agonist** UK 14304, and the calcium ionophore ionomycin. The responses were evaluated both in control conditions and after 30 min of exposure to three different levels of **insulin** (30, 100, and 500 .mu.U/mL). **Insulin** failed to modify the phenylephrine aortic contractions and the relaxations induced by acetylcholine, ADP, and ionomycin. In contrast, both 100 and 500 .mu.U/mL **insulin** were able to potentiate the UK 14304-induced vasorelaxation (+96% and +91%, resp.). Pertussis toxin, which causes .alpha.2-adrenergic receptor Gi uncoupling, reduced the .alpha.2-adrenergic vasorelaxation and prevented the **insulin** potentiation of the response to UK 14304. Furthermore, in primary cultured aortic endothelial cells from WKY, we evaluated the conversion of [3H]arginine to [3H]citrulline in response to acetylcholine, ionomycin, and UK 14304, both in control conditions and during **insulin** exposure. Again, **insulin** did not affect basal citrulline prodn. or the increase induced by acetylcholine and ionomycin, whereas it potentiated the response to UK 14304. Finally, in aortic rings of spontaneously hypertensive rats, **insulin** treatment (100 and 500 .mu.U/mL) was unable to enhance the .alpha.2-adrenergic vasodilator response; in vascular endothelial cells from spontaneously hypertensive rats, **insulin** did not potentiate the increase in citrulline prodn. evoked by UK 14304. In conclusion, **insulin** selectively enhances .alpha.2-adrenergic endothelial vasorelaxation through a pertussis toxin-**sensitive** mechanism, by potentiating endothelial **nitric oxide** prodn. This vasorelaxant mechanism is altered in spontaneously hypertensive rats.

L2 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB A review, with 52 refs. It is well documented that **insulin** has relevant vasoactive properties. In humans, systemic **insulin** infusion by the euglycemic clamp technique causes a dose-dependent increment in peripheral blood flow, suggesting a vasodilatory activity of the hormone. However **insulin** is not a direct relaxing compd. since when it is directly injected into the brachial artery it does not increase forearm blood flow. Therefore it is conceivable that **insulin** acts as a modulator of vascular reactivity. Both in animals and humans **insulin** can attenuate the vasoconstrictor effect of adrenergic (noradrenaline, phenylephrine) and non-adrenergic (angiotensin II) mediators. Therefore it is now accepted that **insulin** blunts vasoconstriction by a non-specific mechanism. Moreover, **resistance** to this anti-vasoconstrictor effect of the hormone has been hypothesized as a possible mechanism responsible for high blood-pressure values assocd. with the **insulin** **resistance** states. Besides antagonizing vasoconstrictor stimuli, **insulin** also potentiates vascular relaxation, mainly when induced by endothelium-dependent **agonists**. In the forearm of normotensive subjects and essential hypertensive patients **insulin** potentiates the vasodilating effect of acetylcholine, an endothelium-dependent vasodilator. However, while in normotensive subjects the facilitating action of **insulin** on endothelium-dependent vasodilation is reversed by L-NMMA and therefore involves the **nitric oxide** pathway, in essential hypertensive patients it is caused by smooth muscle cell hyperpolarization. In summary, available evidence indicates that **insulin**-induced vasodilation is probably mediated by indirect mechanisms, including inhibition of contraction due to differrent stimuli and potentiation of endothelium-dependent relaxation. Whether all these

vascular effects of **insulin** are relevant to metabolic and blood pressure homeostasis remains to be investigated.

ACCESSION NUMBER: 1997:408950 CAPLUS
DOCUMENT NUMBER: 127:76066
TITLE: Insulin and vascular reactivity
AUTHOR(S): Taddei, S.; Salvetti, A.
CORPORATE SOURCE: I Clinica Medica, University of Pisa, Pisa, 56100, Italy
SOURCE: Nutr., Metab. Cardiovasc. Dis. (**1997**), 7(2), 117-123
CODEN: NMCDEE; ISSN: 0939-4753
PUBLISHER: Medikal Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

SO Nutr., Metab. Cardiovasc. Dis. (**1997**), 7(2), 117-123
CODEN: NMCDEE; ISSN: 0939-4753

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L2 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB The **nitric oxide** (NO) **donor** SIN-1 (3-morpholinosydnonimine) induced a concn.-dependent inhibition of the secretory response to glucose. The neg. insulinotropic action of SIN-1 was attenuated by the hypoglycemic sulfonylurea glibenclamide. Moreover, the NO **donor** enhanced 86Rb outflow from perfused islets and reduced the glucose-induced increase in 45Ca outflow. The present data provide further evidence that NO **donors** impair the secretory response to glucose, at least in part, by activating the ATP-sensitive K+ channels.

09/806,989

ACCESSION NUMBER: 1997:313818 CAPLUS
DOCUMENT NUMBER: 127:29365
TITLE: 3-Morpholinosydnonimine as instigator of a glibenclamide-**sensitive** reduction in the **insulin** secretory rate
AUTHOR(S): Antoine, Marie-Helene; Ouedraogo, Raogo; Hermann, Marcel; Sergooris, Jacqueline; Herchuelz, Andre; Lebrun, Philippe
CORPORATE SOURCE: LABORATORY OF PHARMACOLOGY, SCHOOL OF MEDICINE, UNIVERSITE LIBRE DE BRUXELLES, BRUSSELS, B-1070, Belg.
SOURCE: Biochem. Pharmacol. (**1997**), 53(8), 1211-1213
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

TI 3-Morpholinosydnonimine as instigator of a glibenclamide-**sensitive** reduction in the **insulin** secretory rate

SO Biochem. Pharmacol. (**1997**), 53(8), 1211-1213
CODEN: BCPCA6; ISSN: 0006-2952

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IT Potassium channel
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(ATP-**sensitive**; **nitric oxide donor** impairs **insulin** secretory response to glucose by activating ATP-**sensitive** K+ channels)

IT Channel-mediated transport
Islet of Langerhans
Potassium transport (biological)
(**nitric oxide donor** impairs **insulin** secretory response to glucose by activating ATP-**sensitive** K+ channels)

IT 50-99-7, D-Glucose, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**nitric oxide donor** impairs **insulin** secretory response to glucose by activating ATP-**sensitive** K+ channels)

IT 10102-43-9, **Nitric oxide**, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(**nitric oxide donor** impairs **insulin** secretory response to glucose by activating ATP-**sensitive** K+ channels)

IT 7440-09-7, Potassium, biological studies 9004-10-8, **Insulin**, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**nitric oxide donor** impairs **insulin** secretory response to glucose by activating ATP-**sensitive** K+ channels)

L2 ANSWER 10 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB In the present study, we have compared 3-morpholinosydnonimine (SIN-1), which generates **nitric oxide**, superoxide anion and hydrogen peroxide, with two other **nitric oxide donors**, S-nitrosoglutathione (GSNO) and the tetra-iron-sulfur cluster nitrosyl, Roussin's black salt (RBS). We have used the comet assay as a highly **sensitive** method to measure DNA-damaging ability, and also measured inhibition of DNA synthesis and inhibition of **insulin** secretion. We have examd. the effect of superoxide dismutase (SOD) and catalase on each of these endpoints in HIT-T15 cells following a 30-min exposure to the compds. (24 h for DNA synthesis). All compds. produced a significant dose-dependent increase in strand-breakage formation and all inhibited DNA synthesis and glucose-stimulated **insulin** secretion. RBS was the most potent. SOD did not reduce the responses obsd. with any of the compds. Catalase largely prevented DNA strand breakage, inhibition of DNA synthesis and inhibition of **insulin** secretion by SIN-1, but had no effect on responses to GSNO or RBS. Addn. of SOD together with catalase gave no greater protection against SIN-1 than catalase alone. The **nitric oxide** and superoxide anion produced by SIN-1 are thought to combine to form highly reactive peroxynitrite. In addn., H2O2 may be formed in the presence of SIN-1 and may form hydroxyl radical in the presence of a transition metal, such as Fe2+. It appears that in **insulin** -secreting cells, the effects of SIN-1 are largely mediated by this latter mechanism. In contrast, GSNO and RBS appear to act by a different mechanism, not overtly involving reactive oxygen species. GSNO and H2O2 show no significant interaction in the induction of DNA strand breaks. Both **nitric oxide** and H2O2 are effective, directly or indirectly, as DNA strand-breaking agents, inhibitors of DNA synthesis and inhibitors of **insulin** secretion.

ACCESSION NUMBER: 1997:273554 CAPLUS
DOCUMENT NUMBER: 126:339936
TITLE: Use of the comet assay to investigate possible interactions of nitric oxide and reactive oxygen species in the induction of DNA damage and inhibition of function in an insulin-secreting cell line
AUTHOR(S): Delaney, Carol A.; Green, Irene C.; Lowe, Jillian E.; Cunningham, James M.; Butler, Anthony R.; Renton, Louise; D'Costa, Ieta; Green, Michael H. L.
CORPORATE SOURCE: Biochemistry Laboratory, School of Biological Sciences, University of Sussex, Falmer, Brighton, BN1 9QG, UK
SOURCE: Mutation Research (**1997**), 375(2), 137-146
CODEN: MUREAV; ISSN: 0027-5107
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

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CODEN: MUREAV; ISSN: 0027-5107

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L2 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB The authors sought to det. whether hypertriglyceridemia in patients with lipoprotein lipase (LPL) dysfunction is assocd. with endothelial dysfunction in **resistance** vessels of the forearm vasculature. Vasodilator responses to acetylcholine, acting through stimulation of **nitric oxide** (NO) release from the endothelium, are impaired in hypercholesterolemia and normalized by L-arginine, suggesting dysfunction of the L-arginine/NO pathway. Similar abnormalities have been reported in conditions assocd. with hypertriglyceridemia, such as non-**insulin**-dependent diabetes. The relation between endothelial function and plasma triglyceride concns. has, however, not previously been studied in vivo. The authors examd. forearm blood flow responses to brachial artery infusions of acetylcholine (alone and with L-arginine) and nitroprusside (an NO **donor**) in 17 patients with severe hypertriglyceridemia (mean [.+-.SD] plasma triglyceride concn. 1,914.+-.1,288 mg/dL) but normal low d. lipoprotein cholesterol (89.+-.31 mg/dL) and in 34 normolipidemic control subjects. Severe LPL dysfunction was demonstrated in 10 of 17 patients. Acetylcholine (7.5 and 15 .mu.g/min) produced similar forearm blood flow responses in hypertriglyceridemic patients (mean [.+-.SEM] 7.7.+-.0.9 and 10.5.+-.1.2 mL/min per 100 mL) and in control subjects (7.5.+-.0.6 and 11.0.+-.0.8 mL/min per 100 mL, by anal. of variance). Responses to acetylcholine co-infused with L-arginine (10 mg/min) and nitroprusside (3 and 10 .mu.g/min) were also similar in hypertriglyceridemic patients and control subjects (and for acetylcholine with L-arginine and nitroprusside, resp.). The ratio response to acetylcholine/response to nitroprusside differed between hypertriglyceridemic patients and control subjects by only 1%. The study had >90% power (alpha = 0.05) to detect a difference >30% in this ratio. Severe hypertriglyceridemia assocd. with LPL dysfunction is not assocd. with the degree of endothelial dysfunction seen in moderate hypercholesterolemia when responses to acetylcholine are impaired by >40%.

ACCESSION NUMBER: 1997:272525 CAPLUS
DOCUMENT NUMBER: 126:315772
TITLE: Preserved endothelial function in patients with severe hypertriglyceridemia and low functional lipoprotein lipase activity
AUTHOR(S): Chowienczyk, Philip J.; Watts, Gerald F.; Wierzbicki,

Anthony S.; Cockcroft, John R.; Brett, Sally E.; Ritter, James M.
CORPORATE SOURCE: Departments of Clinical Pharmacology and Chemical Pathology, United Medical and Dental School of Guy's and St. Thomas' Hospital, London, SE1 7EH, UK
SOURCE: J. Am. Coll. Cardiol. (**1997**), 29(5), 964-968
CODEN: JACCDI; ISSN: 0735-1097
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
SO J. Am. Coll. Cardiol. (**1997**), 29(5), 964-968
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L2 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2002 ACS
AB Considerable evidence has accumulated suggesting that cytokines, secreted from infiltrating immune cells, mediate the destruction of pancreatic islet B-cells seen in insulin-dependent diabetes mellitus. This action of cytokines results from intracellular generation of **nitric oxide** (NO) which is known to be cytotoxic to both rat and human isolated islets as well as to clonal B-cell lines. However, recent evidence suggests that, for reasons which remain unclear, human islets may be less susceptible than rodent pancreatic B-cells to NO-induced cytotoxicity. We have studied whether this is true for apoptosis, a cell death pathway which can be activated in rodent islets and B-cell lines upon exposure to cytokines or chem. **nitric oxide donors**. We have used a range of apoptosis-inducing agents at high concns., over culture periods of 24-48h, and the results reveal that human islets are consistently less susceptible to induction of apoptosis than

the rodent clonal B-cell lines, RINm5F and HIT-T15.

ACCESSION NUMBER: 1997:167798 CAPLUS
DOCUMENT NUMBER: 126:198020
TITLE: Human pancreatic islets display reduced sensitivity to nitric oxide-induced apoptosis compared to rodent clonal B-cell lines
AUTHOR(S): Loweth, A. C.; Williams, G. T.; Scarpello, J. H. B.; James, R. F. L.; Morgan, N. G.
CORPORATE SOURCE: Cellular Pharmacology Group, Departments of Biological Sciences and Medicine, Keele University, Staffordshire, ST5 5BG, UK
SOURCE: Diabetes Res. (**1996**), 31(6), 231-241
CODEN: DIREEM; ISSN: 0265-5985
PUBLISHER: Teviot-Kimpton Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
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IT Apoptosis
B cell (lymphocyte)
Insulin-dependent diabetes mellitus
Islet of Langerhans
RINm5F cell
(human pancreatic islets display reduced **sensitivity** to nitric oxide-induced apoptosis compared to rodent clonal B-cell lines)

L2 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2002 ACS
AB Interleukin-1.beta. (IL-1.beta.) significantly inhibits **insulin** secretion from glucose stimulated islet cells. The mechanism for this inhibition has been hypothesized to be due to stimulation of the inducible form of **nitric oxide** synthase and a resulting increase in **nitric oxide** (NO) concn. Ways to block the effect of IL-1.beta. have focused on blocking the binding of IL-1.beta. to the IL-1 receptor and the use of antioxidants to neutralize increases in NO. This report focuses on a 33 residue peptide synthesized based on the C-terminal region of the IL-1.beta. mol., a reported binding site of the IL-1.beta. mol., and the redox-cycling antioxidant pyrroloquinoline quinone (PQQ). The 33-residue peptide did not function as an antagonist, but as a weak **agonist**. High concns. of PQQ itself inhibited glucose-dependent **insulin** release while low concns. did not. PQQ had no effect on the actions of IL-1.beta.. Three isosteric and isomeric analogs of PQQ were also investigated. One of the PQQ isomers had an inhibitory effect on **insulin** secretion at low concns.

where PQQ isomers had an inhibitory effect on **insulin** secretion at low concns. where PQQ had no effect. These results reflect the **sensitivity** of islets to oxidative stress.

ACCESSION NUMBER: 1997:40073 CAPLUS
DOCUMENT NUMBER: 126:127173
TITLE: Effects of a 33 residue interleukin-1.beta. peptide and the antioxidant PQQ on interleukin-1.beta.-mediated inhibition of glucose-stimulated insulin release from cultured mouse pancreatic islets
AUTHOR(S): McInerney, Marcia F.; Seidel, Matthew J.; Nguyen, Jaime M. D.; Flynn, Jeffrey C.; Sturm, Noel; Lee, Hyosil; Zhang, Zhoupeng; Tillekeratne, L. M. V.; Hudson, Richard A.
CORPORATE SOURCE: Dep. Med. Biol. chem., Univ. Toledo, Toledo, OH, 43606, USA
SOURCE: Res. Commun. Mol. Pathol. Pharmacol. (**1996**), 94(2), 115-128
CODEN: RCMPE6; ISSN: 1078-0297
PUBLISHER: PJD Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Res. Commun. Mol. Pathol. Pharmacol. (**1996**), 94(2), 115-128
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AB Interleukin-1.beta. (IL-1.beta.) significantly inhibits **insulin** secretion from glucose stimulated islet cells. The mechanism for this inhibition has been hypothesized to be due to stimulation of the inducible form of **nitric oxide** synthase and a resulting increase in **nitric oxide** (NO) concn. Ways to block the effect of IL-1.beta. have focused on blocking the binding of IL-1.beta. to the IL-1 receptor and the use of antioxidants to neutralize increases in NO. This report focuses on a 33 residue peptide synthesized based on the C-terminal region of the IL-1.beta. mol., a reported binding site of the IL-1.beta. mol., and the redox-cycling antioxidant pyrroloquinoline quinone (PQQ). The 33-residue peptide did not function as an antagonist, but as a weak **agonist**. High concns. of PQQ itself inhibited glucose-dependent **insulin** release while low concns. did not. PQQ had no effect on the actions of IL-1.beta.. Three isosteric and isomeric analogs of PQQ were also investigated. One of the PQQ isomers had an inhibitory effect on **insulin** secretion at low concns. where PQQ isomers had an inhibitory effect on **insulin** secretion at low concns. where PQQ had no effect. These results reflect the **sensitivity** of islets to oxidative stress.

L2 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2002 ACS
AB It has been shown very recently that pancreatic islet tissue contains **nitric oxide** (NO-)synthase activity as revealed by both histochem. and immunohistochem. techniques. In the present investigation we have studied, both in vitro and in vivo, the possible influence of NO as a modulator of **insulin** release induced by the sulfonylurea drug, glibenclamide. It was obsd. that the dose-response relationship for glibenclamide-stimulated **insulin** release from isolated mouse islets displayed at least two components. Thus, at a basal glucose concn. of 7 mM the first component of glibenclamide induced **insulin** release started at a concn. of .apprxeq.15 nM of the drug with a plateau at .apprxeq.0.25-10 .mu.M. A further rise in **insulin** release was obsd. at 30 .mu.M glibenclamide. The NO-synthase inhibitor NG-nitro-L-arginine Me ester (L-NAME) lowered the threshold for glibenclamide-induced **insulin** secretion to .apprxeq.4 nM and

significantly enhanced the **insulin** releasing action of glibenclamide up to the plateau level. No effect of L-NAME was obsd. at the plateau-level. However, at high levels of glibenclamide (8-30 .mu.M) (second component) **insulin** release was again increased by NO-synthase inhibition. The intracellular NO-**donor** hydroxylamine dose-dependently inhibited **insulin** release stimulated by a maximal dose (first component) of glibenclamide (0.25 .mu.M). In vivo expts. showed that the acute **insulin** response to an i.v. injection of a half-maximal dose of glibenclamide was significantly enhanced by pretreatment with L-NAME. Similarly, a comparative expt. with a half-maximal dose of glucose showed that NO-synthase inhibition by L-NAME enhanced glucose-induced **insulin** response. L-NAME at the dose employed did not influence basal **insulin** secretion neither in vitro nor in vivo. The results indicate that NO is a neg. modulator of glibenclamide-stimulated **insulin** release and that NO-synthase inhibition enhances sulfonylurea-induced **insulin** response and increases the **sensitivity** of the **insulin** releasing process to low doses of glibenclamide.

ACCESSION NUMBER: 1996:647366 CAPLUS
DOCUMENT NUMBER: 125:316916
TITLE: Modulation of the islet nitric oxide system and sulfonylurea-induced insulin secretion
AUTHOR(S): Aakesson, B.; Lundquist, I.
CORPORATE SOURCE: Department Pharmacology, University Lund, Lund, Swed.
SOURCE: Diabetes Res. (**1996**), 31(3), 91-99
CODEN: DIREEM; ISSN: 0265-5985
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Diabetes Res. (**1996**), 31(3), 91-99
CODEN: DIREEM; ISSN: 0265-5985

AB It has been shown very recently that pancreatic islet tissue contains **nitric oxide** (NO-)synthase activity as revealed by both histochem. and immunohistochem. techniques. In the present investigation we have studied, both in vitro and in vivo, the possible influence of NO as a modulator of **insulin** release induced by the sulfonylurea drug, glibenclamide. It was obsd. that the dose-response relationship for glibenclamide-stimulated **insulin** release from isolated mouse islets displayed at least two components. Thus, at a basal glucose concn. of 7 mM the first component of glibenclamide induced **insulin** release started at a concn. of .apprxeq.15 nM of the drug with a plateau at .apprxeq.0.25-10 .mu.M. A further rise in **insulin** release was obsd. at 30 .mu.M glibenclamide. The NO-synthase inhibitor NG-nitro-L-arginine Me ester (L-NAME) lowered the threshold for glibenclamide-induced **insulin** secretion to .apprxeq.4 nM and significantly enhanced the **insulin** releasing action of glibenclamide up to the plateau level. No effect of L-NAME was obsd. at the plateau-level. However, at high levels of glibenclamide (8-30 .mu.M) (second component) **insulin** release was again increased by NO-synthase inhibition. The intracellular NO-**donor** hydroxylamine dose-dependently inhibited **insulin** release stimulated by a maximal dose (first component) of glibenclamide (0.25 .mu.M). In vivo expts. showed that the acute **insulin** response to an i.v. injection of a half-maximal dose of glibenclamide was significantly enhanced by pretreatment with L-NAME. Similarly, a comparative expt. with a half-maximal dose of glucose showed that NO-synthase inhibition by L-NAME enhanced glucose-induced **insulin** response. L-NAME at the dose employed did not influence basal

insulin secretion neither in vitro nor in vivo. The results indicate that NO is a neg. modulator of glibenclamide-stimulated **insulin** release and that NO-synthase inhibition enhances sulfonylurea-induced **insulin** response and increases the **sensitivity** of the **insulin** releasing process to low doses of glibenclamide.

L2 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB The present study was undertaken to assess the effects of hydroxylamine, a **nitric oxide** (NO) **donor**, on ionic and secretory events in rat pancreatic islets. Hydroxylamine provoked a concn.-dependent inhibition of the glucose-induced **insulin** release. This inhibitory action was counteracted by glibenclamide. Moreover, hydroxylamine increased the rate of 86Rb outflow from perifused islets. This effect persisted in the absence of external Ca2+ but was impaired by glibenclamide. Hydroxylamine decreased 45Ca outflow, [Ca 2+]i and **insulin** output from islets exposed to 16.7 mM glucose and extracellular Ca2+. By contrast, hydroxylamine did not affect the increase in 45Ca outflow and [Ca2+]i evoked by K+ depolarization. These exptl. results suggest that the neg. insulinotropic action of the NO **donor** results, at least in part, from the activation of ATP-**sensitive** K+ channels leading to a decrease in Ca2+ influx and [Ca2+]i. Addnl. mechanisms, however, could also be involved in the NO **donor** modulation of the secretory process.

ACCESSION NUMBER: 1996:609071 CAPLUS
DOCUMENT NUMBER: 125:265645
TITLE: Hydroxylamine, a **nitric oxide donor**, inhibits insulin release and activates K+ATP channels
AUTHOR(S): Antoine, Marie-Helene; Ouedraogo, Raogo; Sergooris, Jacqueline; Hermann, Marcel; Herchuelz, Andre; Lebrun, Philippe
CORPORATE SOURCE: Laboratory of Pharmacology, Universite Libre de Bruxelles, School of Medicine (Bat. GE - CP 617), route de Lennik 808, B-1070, Brussels, Belg.
SOURCE: Eur. J. Pharmacol. (**1996**), 313(3), 229-235
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Hydroxylamine, a **nitric oxide donor**, inhibits insulin release and activates K+ATP channels

SO Eur. J. Pharmacol. (**1996**), 313(3), 229-235
CODEN: EJPHAZ; ISSN: 0014-2999

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donor modulation of the secretory process.

IT Biological transport
Pancreatic islet of Langerhans
(hydroxylamine, a **nitric oxide donor**, inhibits insulin release and activates K+ATP channels)

IT Ion channel
(potassium, ATP-**sensitive**; hydroxylamine, a **nitric oxide donor**, inhibits **insulin** release and activates K+ATP channels)

IT 56-65-5, 5'-ATP, biological studies 7803-49-8, Hydroxylamine, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(hydroxylamine, a **nitric oxide donor**, inhibits insulin release and activates K+ATP channels)

IT 7440-70-2, Calcium, biological studies 9004-10-8, Insulin, biological studies 10102-43-9, **Nitric oxide**, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(hydroxylamine, a **nitric oxide donor**, inhibits insulin release and activates K+ATP channels)

L2 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB **Nitric oxide** (NO) has been proposed as a possible mediator of .beta.-cell damage in human **insulin**-dependent diabetes mellitus (IDDM). This hypothesis is based on in vitro studies with rodent pancreatic islets. In the present study we examd. whether human .beta.-cells are affected by NO. In view of species differences in .beta.-cell **sensitivity** to damaging agents, rat islets were investigated in parallel. Isolated islets were exposed for 90 min to different concns. of three chem. unrelated NO **donors**, 3-morpholino-sydnonimine (SIN-1), S-nitrosoglutathione (GSNO), or heptanitrosyltri-.mu.3-thioxotetraferrate(1-) (RBS). At the end of this incubation, human **insulin** release was mostly similar in control and NO-treated islets but, 48 h later, islet retrieval, islet DNA and **insulin** content, and glucose-induced **insulin** release were markedly lower in islets exposed to NO **donors**. Rat islets were already inhibited during the initial 90 min; 48 h later their loss in .beta.-cell function was similar to that in human islets. Nicotinamide or succinic acid monomethyl ester partially protected against SIN-1 induced islet cell loss, but not against the functional inhibition of human pancreatic islets. Exposure of human or rat islets to RBS was assocd. with significant DNA strand breakage, as judged by the comet assay (single cell gel electrophoresis) and by ultrastructural signs of cell damage. DNA damage was more severe in rat islet cells exposed to similar amts. of RBS. It is concluded that NO **donors** can damage human pancreatic islets, an effect paralleled by induction of nuclear DNA strand breaks.

ACCESSION NUMBER: 1996:280001 CAPLUS
DOCUMENT NUMBER: 125:7289
TITLE: **Nitric oxide donors** decrease the function and survival of human pancreatic islets
AUTHOR(S): Eizirik, D.ecio L.; Delaney, Carol A.; Green, Michael H. L.; Cunningham, James M.; Thorpe, Julian R.; Pipeleers, Daniel G.; Hellerstroem, Claes; Green, Irene C.
CORPORATE SOURCE: Department of Medical Cell Biology, Uppsala University, Biomedicum P.O. Box 571, Uppsala, S-751 23, Swed.

09/806,989

SOURCE: Mol. Cell. Endocrinol. (**1996**), 118(1,2), 71-83
CODEN: MCEND6; ISSN: 0303-7207
DOCUMENT TYPE: Journal
LANGUAGE: English

TI **Nitric oxide donors** decrease the function and survival of human pancreatic islets

SO Mol. Cell. Endocrinol. (**1996**), 118(1,2), 71-83
CODEN: MCEND6; ISSN: 0303-7207

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ST **nitric oxide donor** pancreas diabetes

IT Deoxyribonucleic acids
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(damage, **nitric oxide donors** decrease function and survival of human pancreatic islets)

IT Diabetes mellitus
(insulin-dependent, **nitric oxide donors** decrease function and survival of human pancreatic islets)

IT Pancreatic islet of Langerhans
(.beta.-cell, **nitric oxide donors** decrease function and survival of human pancreatic islets)

IT 98-92-0, Nicotinamide 3878-55-5, Succinic acid monomethyl ester
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(nicotinamide effect on **nitric oxide donor** -induced decrease in function and survival of human pancreatic islets)

IT 12518-87-5, Heptanitrosyltri(sulfido)tetraferrate(1-) 33876-97-0, 3-Morpholino-sydnonimine 57564-91-7, S-Nitrosoglutathione
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**nitric oxide donors** decrease function and survival of human pancreatic islets)

IT 10102-43-9, **Nitric oxide**, biological studies
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BIOL (Biological study); PROC (Process)
(**nitric oxide donors** decrease function

and survival of human pancreatic islets)
IT 9004-10-8, Insulin, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(release; **nitric oxide donors** decrease
function and survival of human pancreatic islets)

L2 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2002 ACS
AB The effect of **insulin** on Na+ pump activity, measured as ouabain-**sensitive** (OS) 86Rb uptake, was studied in the rabbit aorta. In the absence of **insulin**, incubation of endothelium-intact rings for 3 h in a medium contg. a high concn. of glucose (44 mM) decreased OS 86Rb uptake by 42% compared with that obsd. at 5.5 mM glucose. Addn. of **insulin** (0.1-10 mU/mL) increased OS 86Rb uptake at both glucose concns. and eliminated the differences between the groups. **Insulin** also increased OS 86Rb uptake in endothelium-intact and -denuded (ED) rings in the presence of the **nitric oxide** (NO) synthase inhibitor NG-monomethyl-L-arginine. Removal of the endothelium before the incubations did not diminish the **insulin** -induced increase in OS 86Rb uptake, which was concn. dependent. The NO **donor** sodium nitroprusside increased OS 86Rb uptake in ED rings, and its effect and that of **insulin** were additive. Phorbol 12,13-dibutyrate, a direct activator of protein kinase C (PKC), also increased OS 86Rb uptake in ED rings; however, its effect and that of **insulin** were not additive. The PKC inhibitor bisindolylmaleimide totally inhibited **insulin**-induced, but not sodium nitroprusside-induced, increases in OS 86Rb uptake. The results suggest that **insulin** activates the Na+ pump in the aorta and reverses the inhibition of the pump caused by hyperglycemia. This effect of **insulin** can occur at physiol. concns., is independent of endothelium-derived NO, and is presumably mediated by an increase in PKC activity. In contrast, activation of the Na+ pump by NO appears to be independent of PKC.
ACCESSION NUMBER: 1996:266700 CAPLUS
DOCUMENT NUMBER: 124:308111
TITLE: Differential stimulation of Na+ pump activity by insulin and nitric oxide in rabbit aorta
AUTHOR(S): Gupta, Sandeep; Phipps, Krista; Ruderman, Neil B.
CORPORATE SOURCE: Diabetes Metabolism Unit, Boston Univ. School Medicine, Boston, MA, 02118, USA
SOURCE: Am. J. Physiol. (**1996**), 270(4, Pt. 2), H1287-H1293
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Am. J. Physiol. (**1996**), 270(4, Pt. 2), H1287-H1293
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donor sodium nitroprusside increased OS 86Rb uptake in ED rings, and its effect and that of **insulin** were additive. Phorbol 12,13-dibutyrate, a direct activator of protein kinase C (PKC), also increased OS 86Rb uptake in ED rings; however, its effect and that of **insulin** were not additive. The PKC inhibitor bisindolylmaleimide totally inhibited **insulin**-induced, but not sodium nitroprusside-induced, increases in OS 86Rb uptake. The results suggest that **insulin** activates the Na+ pump in the aorta and reverses the inhibition of the pump caused by hyperglycemia. This effect of **insulin** can occur at physiol. concns., is independent of endothelium-derived NO, and is presumably mediated by an increase in PKC activity. In contrast, activation of the Na+ pump by NO appears to be independent of PKC.

L2 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB The ability of .beta. cells to endure assaults may be relevant in the development of **insulin**-dependent diabetes mellitus. This study examines the susceptibility of human pancreatic islets to agents that are cytotoxic for rodent .beta. cells i.e., sodium nitroprusside (NP, a **nitric oxide donor**), streptozotocin (SZ), or alloxan. After 5-8 days in tissue culture, human or rodent islets were exposed for 14 h to NP (50-200 .mu.M) or for 30 min to SZ or alloxan (1-3 mM). Glucose oxidn. by human islets was not reduced by NP, but there was a dose-dependent inhibition in rat (40-90% inhibition) and mouse (10-60% inhibition) islet glucose oxidn. Glucose (16.7 mM)-induced **insulin** release by human islets was not impaired after a 30-min exposure to SZ or alloxan, at concns. that inhibited **insulin** release from rat (30-80% inhibition) or mouse (10-70% inhibition) islets. The viability of human .beta. cells purified by flow cytometry was not affected by SZ or alloxan (5 mM), as judged 1 or 4 days after a 10-min exposure and subsequent culture; these conditions were cytotoxic for rat .beta. cells, with 65-95% dead .beta. cells after 4 days. Human islets transplanted under the kidney capsule of nude mice were not affected by in vivo alloxan exposure, as suggested by preserved graft morphol. and **insulin** content, whereas the endogenous .beta. cells of the transplanted mice were severely damaged (80% decrease in pancreatic **insulin** content and morphol. signs of .beta.-cell destruction). Thus human .beta. cells are **resistant** to NP, SZ, or alloxan at concns. that decrease survival and function of rat or mouse .beta. cells. These marked interspecies differences emphasize the relevance of repair and/or defense mechanisms in .beta.-cell destruction and raise the possibility that such differences may also be present among individuals of the same species.

ACCESSION NUMBER: 1994:627856 CAPLUS
DOCUMENT NUMBER: 121:227856
TITLE: Major species differences between humans and rodents in the susceptibility to pancreatic .beta.-cell injury
AUTHOR(S): Eizirik, Decio L.; Pipeleers, Daniel G.; Ling, Zhidong; Welsh, Nils; Hellerstroem, Claes; Andersson, Arne
CORPORATE SOURCE: Dep. Med. Cell Biol., Uppsala Univ., Uppsala, S-751 23, Swed.
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (**1994**), 91(20), 9253-6
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
SO Proc. Natl. Acad. Sci. U. S. A. (**1994**), 91(20), 9253-6

CODEN: PNASA6; ISSN: 0027-8424

AB The ability of .beta. cells to endure assaults may be relevant in the development of **insulin**-dependent diabetes mellitus. This study examines the susceptibility of human pancreatic islets to agents that are cytotoxic for rodent .beta. cells i.e., sodium nitroprusside (NP, a **nitric oxide donor**), streptozotocin (SZ), or alloxan. After 5-8 days in tissue culture, human or rodent islets were exposed for 14 h to NP (50-200 .mu.M) or for 30 min to SZ or alloxan (1-3 mM). Glucose oxidn. by human islets was not reduced by NP, but there was a dose-dependent inhibition in rat (40-90% inhibition) and mouse (10-60% inhibition) islet glucose oxidn. Glucose (16.7 mM)-induced **insulin** release by human islets was not impaired after a 30-min exposure to SZ or alloxan, at concns. that inhibited **insulin** release from rat (30-80% inhibition) or mouse (10-70% inhibition) islets. The viability of human .beta. cells purified by flow cytometry was not affected by SZ or alloxan (5 mM), as judged 1 or 4 days after a 10-min exposure and subsequent culture; these conditions were cytotoxic for rat .beta. cells, with 65-95% dead .beta. cells after 4 days. Human islets transplanted under the kidney capsule of nude mice were not affected by in vivo alloxan exposure, as suggested by preserved graft morphol. and **insulin** content, whereas the endogenous .beta. cells of the transplanted mice were severely damaged (80% decrease in pancreatic **insulin** content and morphol. signs of .beta.-cell destruction). Thus human .beta. cells are **resistant** to NP, SZ, or alloxan at concns. that decrease survival and function of rat or mouse .beta. cells. These marked interspecies differences emphasize the relevance of repair and/or defense mechanisms in .beta.-cell destruction and raise the possibility that such differences may also be present among individuals of the same species.

L2 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2002 ACS

AB To compare the **sensitivity** of different mammalian cell types towards the cytotoxic action of **nitric oxide**, freshly isolated rat pancreatic islet cells, hepatocytes, resident and activated macrophages, cultured aortic endothelial cells and two murine tumor cell lines were tested for susceptibility towards exogenous **nitric oxide**. Nitroprusside, S-nitroso-N-acetyl-penicillamine and the sydnonimine-deriv. SIN-1 were used as sources for **nitric oxide**. These generate **nitric oxide** by different mechanisms and kinetics. Among the cell types tested the authors found large differences in their susceptibility towards the three **nitric oxide donors**. Islet cells were by far the most **sensitive** of the investigated cells and were completely lysed by all three **nitric oxide donors**. Hepatocytes and endothelial cells were **sensitive** towards nitroprusside but relatively **resistant** towards toxicity of SIN-1 and S-nitroso-N-acetyl-penicillamine. Activated and resident macrophages were lysed by SIN-1, whereas high concns. of nitroprusside and S-nitroso-N-acetyl-penicillamine led to partial cell lysis only. The tumor cell lines were both lysed by SIN-1 but showed differences in their **sensitivity** towards S-nitroso-N-acetyl-penicillamine. **Nitric oxide**, which is produced in large amts. during infection and inflammation, may play an important role in the destruction of islet cells during insulitis leading to **insulin**-dependent diabetes mellitus.

ACCESSION NUMBER: 1993:667955 CAPLUS
DOCUMENT NUMBER: 119:267955
TITLE: Pancreatic islet cells are highly susceptible towards

the cytotoxic effects of chemically generated nitric oxide

AUTHOR(S): Kroencke, Klaus-D.; Brenner, Heinz-H.; Rodriguez, Maria-L.; Etzkorn, Kai; Noack, Eike A.; Kolb, Hubert; Kolb-Bachofen, Victoria

CORPORATE SOURCE: Institute of Immunobiology, Department of Medicine, Heinrich-Heine-University of, Dusseldorf, Germany

SOURCE: Biochim. Biophys. Acta (**1993**), 1182(2), 221-9
CODEN: BBACAQ; ISSN: 0006-3002

DOCUMENT TYPE: Journal
LANGUAGE: English

SO Biochim. Biophys. Acta (**1993**), 1182(2), 221-9
CODEN: BBACAQ; ISSN: 0006-3002

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